Primary thyroid cancer after a first tumour in childhood (the Childhood Cancer Survivor Study): a nested case-control study

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See Comment page 1986

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Summary

Background **Survivors of malignant disease in childhood who have had radiotherapy to the head, neck, or upper thorax have an increased risk of subsequent primary thyroid cancer, but the magnitude of risk over the therapeutic dose range has not been well established. We aimed to quantify the long-term risk of thyroid cancer after radiotherapy and chemotherapy.**

Methods **In a nested case-control study, 69 cases with pathologically confirmed thyroid cancer and 265 matched controls without thyroid cancer were identified from 14 054 5-year survivors of cancer during childhood from the Childhood Cancer Survivor Study cohort. Childhood cancers were diagnosed between 1970 and 1986 with cohort follow-up to 2000.**

Findings **Risk of thyroid cancer increased with radiation doses up to 20–29 Gy (odds ratio 9·8 [95% CI 3·2–34·8]). At doses greater than 30 Gy, a fall in the dose-response relation was seen. Both the increased and decreased risks were more pronounced in those diagnosed with a first primary malignant disease before age 10 years than in those older than 10 years. Furthermore, the fall in risk remained when those diagnosed with Hodgkin's lymphoma were excluded. Chemotherapy for the first cancer was not associated with thyroid-cancer risk, and it did not modify the effect of radiotherapy. 29 (42%) cases had a first diagnosis of Hodgkin's lymphoma compared with 49 (19%) controls. 11 (42%) of those who had Hodgkin's lymphoma had subsequent thyroid cancers smaller than 1 cm compared with six (17%) of those who had other types of childhood cancer (p=0·07).**

Interpretation **The reduction in radiation dose-response for risk of thyroid cancer after childhood exposure to thyroid doses higher than 30 Gy is consistent with a cell-killing effect. Standard long-term follow-up of patients who have had Hodgkin's lymphoma for detection of thyroid cancer should also be undertaken for survivors of any cancer during childhood who received radiotherapy to the thorax or head and neck region.**

Introduction

Modern combined-modality treatments have vastly improved survival for children with malignant disease,[1] and an understanding of the late effects of treatment is important for continued medical care. However, long-term survivors of those who had malignant disease in childhood have an increased incidence of subsequent primary thyroid cancer up to several decades after receiving radiotherapy for Hodgkin's lymphoma, acute leukaemia, brain tumour, neuroblastoma, and non-Hodgkin's lymphoma.[2–9] Most thyroid cancers are curable, but a second cancer in an individual surviving a first cancer is a substantial psychological and physical burden.

The magnitude of risk of subsequent primary thyroid cancer over the range of radiotherapy doses is uncertain because dose-response analyses of only 14 and 22 cases have been done.[10,11] The findings showed a linear dose-response at low doses that seemed to flatten above 10 Gy, but linearity could not be ruled out.[12]

Large studies are needed to increase confidence in the shape of the dose-response curve,[13] especially for doses greater than 10 Gy where the effect of cell killing in thyroid tissue is more likely.[14] Therefore we have done a nested case-control study of treatment-related thyroid cancers in the Childhood Cancer Survivor Study (CCSS) cohort. This group consists of 14 054 individuals who had cancer in childhood and who survived for 5 years or longer.[15] Collectively, the CCSS cohort has more than three times the number of secondary thyroid cancers for analysis than those of previous studies, has detailed treatment information for the first cancer, and received radiation doses to the thyroid gland ranging from 0 Gy to more than 50 Gy.

Methods

Patients

Individuals were eligible if they were diagnosed before age 21 years with leukaemia, CNS tumour, Hodgkin's lymphoma, non-Hodgkin lymphoma, kidney tumour, neuroblastoma, soft-tissue sarcoma, or bone cancer during 1970–86 at one of 25 institutions in the USA or Canada, and if they had survived for at least 5 years.[15] The CCSS research protocol and procedures were approved by the human subjects committees at each participating institution. Informed consent was

obtained for all patients. A baseline, self-administered questionnaire sent in 1994 obtained data for demographic characteristics, education, income, employment history, marital status, height, weight, personal-health habits, history of family cancer, use of medications, reproductive history, new malignant disorders, and other health outcomes.[16] A second survey mailed to cohort members in 2000 elicited further, although less extensive, information.

Cases were people with a primary thyroid cancer diagnosed 5 years or later after a first childhood tumour. Participants reporting a thyroid cancer on the first or second survey were asked to return a signed medical-record release. Pathology reports were obtained, and thyroid cancers were confirmed by CCSS pathologists (n=72).[7]

Controls were those free of thyroid cancer and with an intact thyroid gland, and were selected by stratified random sampling with a ratio of four controls to one case matched for: sex, age at time of diagnosis of first primary cancer (no more than 2 years older or younger than the case), and follow-up interval (controls must have survived their first primary cancer and been at risk of thyroid cancer at least to the case's age at thyroid-cancer diagnosis). 288 controls were selected by this method, but one control had had thyroid tissue removed during the risk period and was therefore excluded. Controls were not matched by the type of first primary cancer, the calendar year it occurred, the treating institution, or ethnic origin. If the control set (any of the four controls matched to one case) did not include a person with the same first primary tumour as the case, a fifth control was selected who was matched for type of first cancer, sex, age at diagnosis, and survival. 27 fifth controls were selected; they were included only in analyses restricted to cases and controls diagnosed with the same type of first cancer.

Procedures

Copies of radiotherapy records for the first cancer diagnosis and treatment, as well as for any further treatment in intervening years for recurrent or new primary cancers, were obtained from the treating institution by uniform data-abstraction procedures and forwarded to the collaborating medical physicist. For every patient, we calculated the total dose of radiation given within the matched time interval, including that for treatment of new primary cancers other than thyroid cancer during the risk period. Radiation dose received in the 5 years before thyroid-cancer diagnosis (or equivalent date in controls) was excluded because other studies[13,17] have indicated a minimum 5-year latency for radiation-induced thyroid cancer—a criterion that led to the exclusion of some dose information for four patients.

Doses to the left and right lobes of the thyroid gland and to the pituitary gland were calculated separately. We assessed the dose to the pituitary gland because cranial irradiation might perturb the hypothalamic–pituitary axis and suppress production of thyroid-stimulating hormone,[18,19] potentially decreasing subsequent thyroid-cancer risk.

Doses absorbed by organs—including doses from radiation scatter—were estimated by one of three methods, depending on the proximity of the organs to treatment beams. First, if the organ was outside the nearest treatment field, doses were based on out-of-

	Cases (n=72)	Controls (n=287)
Sex†		
Male	21 (29%)*	84 (29%)*
Female	51 (71%)	203 (71%)
Ethnic origin†		
White	64 (89%)	259 (90%)
Black	1 (1%)	12 (4%)
Hispanic	6 (8%)	11 (4%)
Asian	1 (1%)	3 (1%)
Other or not specified	0 (0%)	2 (1%)
Age at first cancer diagnosis (years)†		
<5	14 (19%)	61 (21%)
5–9	15 (21%)	56 (20%)
10–14	30 (42%)	120 (42%)
15–20	13 (18%)	50 (17%)
Calendar year of first cancer diagnosis		
1970–73	21 (29%)	61 (21%)
1974–77	20 (28%)	85 (30%)
1978–81	20 (28%)	82 (29%)
1982–86	11 (15%)	59 (21%)
Age at thyroid cancer diagnosis (years)		
<15	6 (8%)	..
15–19	12 (17%)	..
20–24	16 (22%)	..
25–29	14 (19%)	..
30–34	16 (22%)	..
≥35	8 (11%)	
Time between first primary and thyroid cancer diagnosis (years)		
5–9	11 (15%)	..
10–14	20 (28%)	..
15–19	27 (38%)	..
>20	14 (19%)	..
Calendar year of thyroid cancer diagnosis		
1976–84	6 (8%)	..
1985–89	12 (17%)	..
1990–94	23 (32%)	..
1995–2001	31 (43%)	..
Reported thyroid nodules 1 year or more before thyroid cancer diagnosis‡		
No	54 (75%)	269 (94%)
Yes	8 (11%)	13 (5%)
Unknown§	10 (14%)	5 (2%)
Reported underactive thyroid gland 1 year or more before diagnosis‡		
No	52 (72%)	250 (87%)
Yes	9 (13%)	29 (10%)
Unknown§	11 (15%)	8 (3%)
Reported overactive thyroid gland 1 year or more before diagnosis‡		
No	62 (86%)	272 (95%)
Yes	3 (4%)	9 (3%)
Unknown§	7 (10%)	6 (2%)

Data are number (%). *Might not add up to 100% because of rounding. †Matching factor. ‡An equivalent cut-off age was used for controls on basis of case age at diagnosis. §Respondent indicated "not sure" to the question or question answered.

Table 1: **Characteristics of thyroid cancer cases and matched controls**

beam measurements in a water phantom.[20,21] Second, the dose to organs in the beam was derived by use of standard radiotherapy techniques.[22] Third, if the organ was shielded by physical blocking, treatment-planning-system calculations were done.[23] Patients' dosimetry information was assigned a quality score, indicating the certainty of the dose estimates (ie, high, moderate, fair, or inadequate) on the basis of the completeness of the records received and the proximity of the thyroid gland to the treatment beam.

Abstraction of chemotherapy information (ie, whether chemotherapy had been given [yes/no], method used, and cumulative doses) from medical records was done by uniform collection procedures.[16] We estimated risk for each chemotherapy agent separately if at least five cases and five controls underwent that treatment. We assessed the dose-response for any that was associated with a significantly increased risk for the yes/no indicator ($p<0·05$) adjusted for radiation dose. Similar agents were classified as alkylating agents, anthracyclines, or epipodophyllotoxins; no cases were treated with platinum compounds and thus these agents could not be assessed.

Statistical analysis

We used conditional regression analysis and calculated odds ratios to estimate the relative risk for radiotherapy and chemotherapy.[24] The relation between lobe-specific thyroid-radiation dose and thyroid-cancer risk was modelled by several methods. We assessed whether risk of thyroid cancer increased with rising radiation dose across the whole dose range in a simple linear model. We then tested for a reduction in risk at higher doses by use of linear-exponential models. Furthermore, we assessed whether the increased risk, decreased risk, or both could be better defined by a linear-quadratic term.

All models were derived from a larger, more general model for radiation-induced carcinogenesis on the basis of previous data and radiobiological theory, in which cancer risk increases linearly at low doses but potentially falls at high doses (ie, the cell-killing effect).[25,26] The linear parameter in these models is the excess relative risk (ERR) at low doses (equal to the relative risk minus one and expressed per Gy). For these analyses we used the linear-exponential model because it provided the simplest and most meaningful description of the data compared with the linear model ($p=0·0006$). A linear-quadratic model also fit better than the linear model, but did not fit as well as the linear-exponential model.

Statistical tests were done by the likelihood ratio test. When adjusting for the effect of the first cancer, we formed three groups, consisting of Hodgkin's lymphoma, leukaemia, and other cancers. We did separate analyses of all cases and all controls, and of cases and controls who had the same type of first cancer. By use of the linear-exponential model, we assessed radiation dose and thyroid-cancer risk by age at first cancer diagnosis (as a surrogate for age at radiation exposure), type of first cancer, sex, latency, attained age, and by type of chemotherapy (ie, alkylating agents, anthracyclines, and epipodophyllotoxins) within the lower dose range (ie, less than 15 Gy) where the dose-response was assumed to be linear.

Role of the funding source

The study sponsors had no involvement in the study design; collection, analysis, or interpretation of the data; or in the writing of this report. The corresponding author had full access to all the data in the study and had full responsibility for the decision to submit the article for publication.

Results

Of the 72 pathologically confirmed subsequent primary thyroid cancers, 56 (78%) were papillary, 11 (15%) follicular, and five (7%) of other or unspecified histology. Table 1 shows characteristics of cases and matched controls. Secondary thyroid-cancer diagnoses were fairly evenly distributed for 5-year age intervals spanning 15–34 year olds, with 66% of thyroid cancers

	Cases (n=69)*	Controls (n=265)*	Mean age at first cancer diagnosis (years)		Radiotherapy for first cancer		Mean radiation dose to thyroid (Gy)†	
			Cases	Controls	Cases	Controls	Cases	Controls
Type of first tumour or cancer								
Leukaemia	14 (20%)	86 (33%)	5·5 (3·4)	7·8 (4·3)	14 (100%)	69 (80%)	13·7 (7·5)	3·6 (6·4)
Bone	5 (7%)	26 (10%)	13·6 (4·4)	12·0 (4·0)	3(60%)	11 (42%)	10·3 (5·3)	3·5 (5·7)
Brain, CNS	7 (10%)	35 (13%)	9·1 (2·7)	7·6 (5·0)	7(100%)	27 (77%)	17·5 (14·6)	10·5 (13·4)
Hodgkin's lymphoma	29 (42%)	49 (19%)	12·9 (3·3)	14·0 (3·2)	27 (93%)	48 (98%)	36·9 (8·7)	36·3 (12·7)
Kidney (Wilms') tumour	2 (3%)	10 (4%)	1·0 (1·4)	3·4 (2·7)	1 (50%)	7 (70%)	12·7 (0)	1·5 (3·1)
Neuroblastoma	4 (6%)	9 (3%)	0·3 (0·5)	3·4 (6·3)	4 (100%)	4 (44%)	8·5 (7·9)	2·9 (4·8)
Non-Hodgkin's lymphoma	5 (7%)	15 (6%)	13·0 (3·0)	10·0 (4·1)	5 (100%)	14 (93%)	22·4 (4·1)	16·0 (18·2)
Soft-tissue sarcoma	3 (4%)	35 (13%)	9·3 (6·0)	11·7 (5·2)	2 (67%)	21 (60%)	15·3 (9·5)	2·8 (9·1)

Data are number (%) or mean (SD). *Excluding three cases (and their 12 matched controls) and ten controls with missing or incomplete dose information. †Radiation exposure to the lobe where cancer first developed (if known) and the same lobe for controls. If thyroid cancer was multifocal or if it was not possible to determine right or left lobe of origin (n=28), then mean dose for both lobes used. Mean dose was calculated for 63 cases and 209 controls given radiotherapy; doses ranged from 0·01 Gy to 62·4 Gy.

Table 2: **Characteristics of thyroid cancer cases and matched controls by type of first cancer**

diagnosed 10–19 years after the first cancer (median 15·9 years). A self-reported history of thyroid nodules 1 year or more before age of thyroid-cancer diagnosis was more frequent in cases compared with an equivalent age in matched controls. Self-reported frequency of an underactive or overactive thyroid gland was much the same for cases and controls.

Information about radiotherapy was inadequate for three cases; these cases and 12 matched controls were excluded. Ten controls with inadequate dosimetry were also excluded. 62 (86%) cases and 244 (85%) controls had high or moderate quality scores. For five cases, thyroid cancer was the third malignant disease (intervening cancers were melanoma of the head and neck, fibrosarcoma of the head and neck, unspecified osteosarcoma of long bone, meningioma, and plasmacytoma of the head and neck). Two cases had had radiotherapy for a second cancer, but both were treated within the 5-year period before diagnosis and these doses were not included in analyses. Eight controls had a second malignant disorder during the risk period that corresponded to the matched case (cancers were breast [n=4], uterus unspecified, melanoma of the lower limb, tongue, and primitive neuroectodermal tumour of the spinal cord). Two controls had had radiotherapy for a second cancer, but in the 5-year interval before diagnosis of the corresponding thyroid-cancer case and thus these thyroid doses were not included in analyses.

Table 2 shows selected clinical characteristics. For cases, the largest proportion of first-cancer diagnoses was Hodgkin's lymphoma, whereas this diagnosis was less than half as frequent in controls. Leukaemia was the most common first-cancer diagnosis in controls (about a third) compared with a fifth in cases. The number of cases and controls who had had radiotherapy for the first cancer did not differ much, but cases received higher mean radiation doses to the thyroid gland than did controls for most types of first cancers. However, for Hodgkin's lymphoma the difference in mean dose between cases and controls was negligible (36·9 Gy *vs* 36·3 Gy), but the mean dose was much higher than for any other type of first cancer. Because Hodgkin's lymphoma is usually diagnosed in adolescence, mean radiation dose to the thyroid increased with age at diagnosis of first cancer in our study; mean radiation dose in controls was 4·9 Gy for patients younger than 5 years, 6·7 Gy for those 5–9 years, 15·0 for those 10–14 years, and 23·6 Gy those 15 years or older.

Table 3 shows the relation of secondary thyroid carcinoma to radiotherapy and chemotherapy, adjusted for type of first cancer (ie, Hodgkin's lymphoma, leukaemia, or other). Inclusion of radiation doses received in 5 years before a diagnosis of thyroid cancer or in the corresponding matched time interval in controls did not affect the results (data not shown). Any

	Cases* (n=68)	Controls* (n=261)	Odds ratio (95% CI)
Radiotherapy†			
No	6 (9%)	64 (25%)	1·0
Yes	62 (91%)	197 (76%)	2·6 (1·1–7·1)
Radiation to thyroid gland (Gy)†‡			
No radiotherapy treatment	6 (9%)	64 (25%)	1·0
>0–<10	11 (16%)	121 (46%)	1·1 (0·4–3·3)
10–<20	12 (18%)	18 (7%)	6·9 (2·3–23·8)
20–<30	18 (27%)	17 (7%)	9·8 (3·2–34·8)
30–<40	14 (21%)	19 (7%)	3·4 (0·8–14·7)
⩾40	7 (10%)	22 (8%)	1·6 (0·3–7·8)
Chemotherapy§			
No chemotherapy	14 (21%)	51 (21%)	1·0
Any chemotherapy	54 (79%)	198 (80%)	1·1 (0·5–2·6)
Alkylating agents§¶‖			
No	24 (35%)	127 (51%)	1·0
Yes	44 (65%)	122 (49%)	1·3 (0·6–2·5)
Anthracyclines§¶**			
No	44 (65%)	154 (62%)	1·0
Yes	24 (35%)	95 (38%)	1·8 (0·9–4·0)
Epipodophyllotoxins¶††			
No	64 (94%)	237 (95%)	1·0
Yes	4 (6%)	12 (5%)	1·4 (0·3–6·3)
Radiation to pituitary gland (Gy)§‡‡			
>0–<10	38 (56%)	92 (35%)	1·0
10–<20	5 (7%)	31 (12%)	1·3 (0·3–5·1)
20–<30	11 (16%)	41 (16%)	1·9 (0·5–7·6)
30–<40	4 (6%)	12 (5%)	1·4 (0·3–6·6)
⩾40	4 (6%)	21 (8%)	1·1 (0·2–4·1)

Data are number (%). *Excluding three cases (and their 12 matched controls) and ten controls with missing or incomplete dose information; one case and four controls were uninformative for this analysis because they all had the same radiation dose. Percentages may not add to 100% because of rounding. †Adjusted for type of first cancer. ‡Radiation exposure to the lobe where cancer first developed (if known) and the same lobe for controls. If thyroid cancer was multifocal or if it was not possible to determine right or left lobe of origin (n=28), then mean dose for both lobes used. §Adjusted for type of first cancer and radiation dose to thyroid. ¶12 controls excluded from analyses because no information on chemotherapy was available. ‖Alkylating agents included diaziquone, carmustine, lomustine, chlorambucil, procarbazine, cyclophosphamide, dacarbazine, ifosfamide, melphalan, chlormethine, and busulfan. **Anthracyclines included: daunorubicin, doxorubicin, and idarubicin. ††Epipodophyllotoxins included: teniposide and etoposide. ‡‡Reference category of "no radiation treatment" for pituitary dose was already in the model as the reference category for thyroid dose and therefore cannot be used in models that contain both thyroid and pituitary radiation dose.

Table 3: **Risk of second thyroid cancer by radiotherapy and chemotherapy**

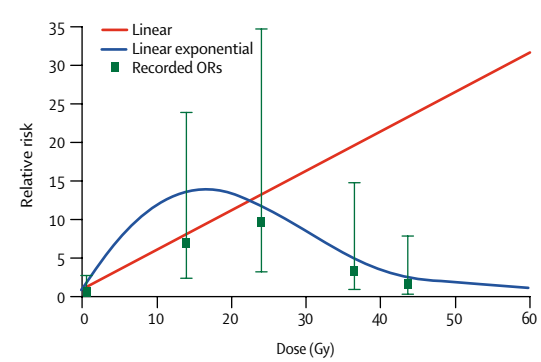

Figure 1: **Thyroid-cancer risk by radiation dose in cases and controls after adjustment for first cancer**
Linear dose-response model for relative risk calculated as: 1+0·5117(dose). Linear-exponential dose-response model for relative risk calculated as 1+1·316[dose]e(−0·00189[dose×dose]). Vertical lines=95% CIs for OR.

radiotherapy for the first cancer was associated with an increased risk of subsequent thyroid cancer compared with children who did not receive radiation (p=0·028). Risk of thyroid cancer increased with radiation dose to the thyroid gland for doses up to 29 Gy and decreased for doses greater than 30 Gy.

Data for chemotherapy use were available for 49 agents, and cumulative chemotherapy doses within the matched time interval were available for 22 of these.[15] After adjustment for radiation dose and first cancer, chemotherapy did not significantly affect risk of thyroid cancer (table 3). No significant trend in the dose-response was noted for alkylating agents or anthracyclines (data not shown). Several agents (including doxorubicin and dactinomycin) were assessed individually, but had no effect on thyroid-cancer risk. With adjustment for dose to the thyroid gland, radiation dose to the pituitary gland was not associated with thyroid-cancer risk (table 3).

Figure 1 shows the plotted linear and the linear-exponential dose-response models with the observed ORs and CIs for risk of secondary thyroid cancer. Using the linear-exponential model, the linear slope at low radiation doses (ie, <15 Gy), corresponding to the ERR, was 1·32 per Gy (95% CI 0·44–4·06). The shape of the dose-response curve in analyses that included only controls who had the same type of first cancer as their matched case (n=98) was qualitatively similar to that of figure 1, although the curves ascended more steeply at low doses, and the CIs were much wider (ERR 4·2 per Gy, [95% CI 0·7–24·9]). Odds ratios and parameter estimates remained much the same after removal of five cases and eight controls who had another malignant disorder during the risk period and after removal of 20 cases and 42 controls for whom the precision of the estimated thyroid doses was of moderate or fair quality.

Because age at first cancer diagnosis, type of first cancer, and radiation dose to the thyroid were highly

Radiation dose to thyroid gland, Gy	Cases* (n=68)	Controls* (n=261)	Odds ratio (95% CI)
Age at first cancer diagnosis (years)†			
<10			
No radiotherapy	2	36	1·0
>0–<10	9	54	2·9 (0·7–19·7)
10–<20	10	8	16·3 (3·5–125)
20–<30	5	7	16·3 (2·3–182)
30–<40	2	2	12·7 (0·9–203)
⩾40	0	2	0
⩾10			
No radiotherapy	4	30	1·0
>0–<10	2	64	0·3 (<0·1–1·7)
10–<20	2	10	2·9 (0·3–23·6)
20–<30	13	10	4·8 (1·1–23·7)
30–<40	12	17	1·5 (0·3–8·8)
⩾40 Gy	7	21	0·8 (0·1–5·3)
Type of first primary cancer			
Hodgkin's lymphoma			
No radiotherapy	2	1	1·0
>0–<10	0	3	0
10–<20	0	1	0
20–<30	6	5	Undefined‡ (0·2–∞)
30–<40	13	16	1·3 (<0·1–52·0)
⩾40	7	19	0·4 (<0·1–12·1)
Other cancer			
No radiotherapy	4	63	1·0
>0–<10	11	118	1·8 (0·6–7·0)
10–<20	12	17	11·3 (3·1–51·3)
20–<30	12	12	21·2 (4·8–122)
30–<40	1	3	7·8 (0·3–125)
⩾40	0	3	0
Sex†			
Men			
No radiotherapy	2	17	1·0
>0–<10	2	38	0·4 (<0·1–3·7)
10–<20	4	7	3·2 (0·4–36·7)
20–<30	7	6	5·3 (0·9–52·7)
30–<40	4	5	1·1 (0·1–14·2)
⩾40	2	8	0·3 (<0·1–5·6)
Women			
No radiotherapy	4	47	1·0
>0–<10	9	83	1·5 (0·4–6·2)
10–<20	8	11	10·7 (2·6–54·3)
20–<30	11	11	19·0 (4·0–114)
30–<40	10	14	10·1 (1·5–83·9)
⩾40	5	14	6·3 (0·7–65·6)
Latency†			
Less than 15 years			
No radiotherapy	3	41	1·0 (reference)
>0–<10	7	67	1·3 (0·3–6·5)
10–<20	8	6	12·6 (3·0–68·8)
20–<30	8	10	10·6 (2·2–64·8)
30–<40	6	9	7·4 (1·0–66·8)
⩾40	3	4	9·3 (0·8–135)
15 years or more			
No radiotherapy	3	23	1·0 (reference)
>0–<10	4	54	0·7 (0·1–4·1)
10–<20	4	12	3·2 (0·4–29·0)
20–<30	10	7	9·8 (1·8–71·6)
30–<40	8	10	1·6 (0·2–13·5)
⩾40	4	18	0·3 (<0·1–3·2)
Attained age†			
Less than 25 years			
No radiotherapy	3	38	1·0 (reference)
>0–<10	9	70	1·9 (0·5–8·7)
10–<20	9	9	10·2 (2·6–53·0)
20–<30	6	11	7·5 (1·4–49·0)
30–<40	5	5	8·5 (1·0–88·8)
⩾40	1	1	5·7 (0·2–146)
25 years or older			
No radiotherapy	3	26	1·0 (reference)
>0–<10	2	50	0·3 (<0·1–2·1)
10–<20	3	9	7·7 (0·8–99·8)
20–<30	12	7	13·4 (2·4–111)
30–<40	9	14	1·0 (0·1–7·8)
⩾40	6	21	0·4 (0·0–3·3)

*Excluding three cases (and their 12 matched controls) and ten controls with missing or incomplete dose information; one case and four controls were uninformative for this analysis because they all had the same radiation dose. †Adjusted for first cancer (Hodgkin's lymphoma, leukaemia, or other). ‡Case and control sets had equivalent radiation doses; OR for matched sets lacking a discordant pair cannot be calculated.

Table 4: **Radiation dose and risk of thyroid cancer by: age at diagnosis of first cancer, type of first cancer, sex, latency, and attained age**

correlated, we assessed the dose-response relation separately by age at first cancer diagnosis (<10 years and ⩾10 years) and by type of first cancer (Hodgkin's lymphoma *vs* other cancers). Patients younger than 10 years had substantially higher thyroid-cancer risk over the entire radiation-dose range than did patients aged 10 years or older (table 4). Figure 2 shows plots of the linear-exponential dose-response curves for those diagnosed with a first cancer when younger than 10 years versus those 10 years or older. Although both plots show rising risks that fall at doses above 30 Gy for subsequent primary thyriod cancer, for those younger than 10 years at first cancer diagnosis, the ascending and descending slopes were much steeper than for those diagnosed at 10 years or older. At low doses (<15 Gy), our estimate of ERR for those younger than 10 years was 3·5 per Gy (95% CI 0·8–29·5) compared with 0·9 (0·2–4·2) for those diagnosed with a first cancer at 10 years or older, but the difference was not significant (p=0·37).

Assessment by type of first cancer (ie, Hodgkin's lymphoma *vs* all others) showed that only a small proportion of patients with Hodgkin's lymphoma had no or low radiation dose to the thyroid, whereas the opposite was true for patients who had other cancers in childhood. The relative risk of thyroid cancer did not exceed unity in the radiation dose strata that had sufficient numbers of patients with Hodgkin's lymphoma to allow calculations. For other types of cancer, risk peaked at 20–29 Gy, although CIs were very wide (table 4). For doses less than 15 Gy, ERR from the linear-exponential dose-response model for Hodgkin's lymphoma was 0·1 per Gy compared with 2·2 per Gy for all other cancers (p=0·04). The slope of the radiation dose-response for doses less than 15 Gy was 0·9 per Gy for men and 1·6 per Gy for women, p=0·59. However, the relative risk for subsequent primary thyroid cancer in women was consistently higher than the risk in men in all dose categories (table 4).

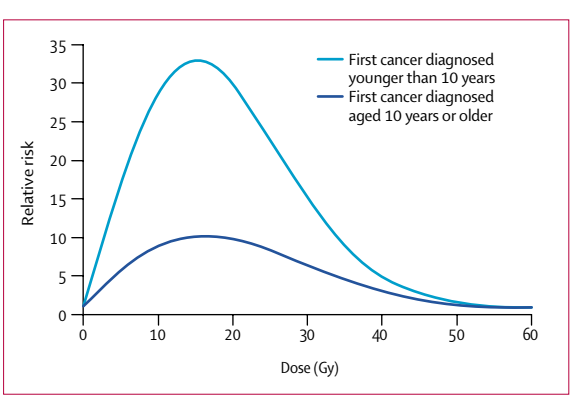

Figure 2: **Thyroid-cancer risk by radiation dose according to age at diagnosis of first cancer**
Dose-response model for relative risk in those younger than 10 years calculated by: 1+3·493(dose)e(−0·002226[dose×dose]). Dose-response model for relative risk in those 10 years or older calculated by 1+0·9362(dose)e(−0·001846[dose×dose]).

	Type of first cancer		
	Hodgkin's lymphoma* (n=26)	Leukaemia (n=15)	Other† (n=20)
Tumour size (largest dimension, cm)‡			
0·1–0·9	11 (42%)	3 (20%)	3 (15%)
>1·0	12 (46%)	7 (47%)	13 (65%)
Nodal metastasis	3 (12%)	5 (33%)	4 (20%)

*p=0·07 for Hodgkin's lymphoma versus all other types of first cancer, Pearson χ^2 test. †Other first cancers include bone, CNS, Wilms', neuroblastoma, non-Hodgkin lymphoma, and soft-tissue sarcoma. ‡Does not include 11 cases for which tumour size was not stated (n=8) or the pathology report was missing or incomplete (n=3).

Table 5: **Size of thyroid cancer and lymph-node involvement based on surgical pathology report by type of first cancer diagnosis**

Relative risks of thyroid cancer for radiation treatment (yes *vs* no) by time since first childhood tumour (latency) were 2·0 (95% CI 0·3–38·9) for 5–9 years, 4·9 (1·5–22·3) for 10–19 years, and 0·9 (0·2–6·1) for 20 years or more. Risk of thyroid cancer tended to be higher for a latency of less than 15 years and for attained age in those younger than 25 years (table 4). ERR for doses less than 15 Gy were 1·6 per Gy for <15 years' latency *vs* 1·1 per Gy for ⩾15 years' latency (p=0·74), and 1·6 per Gy for patients <25 years *vs* 1·1 for those ⩾25 years (p=0·30).

We also assessed the risk of thyroid cancer associated with the type of first cancer—ie, after accounting for the effect of radiation treatment and after using leukaemia in childhood as the reference category. After adjustment for radiation dose and age at the time of first cancer diagnosis as a modifier of radiation exposure, risk of subsequent thyroid cancer for those that had had Hodgkin's lymphoma (29 cases) and neuroblastoma (four cases) remained significant (OR 6·3 [95% CI 1·7–24·0] and 7·4 [1·0–54·7], respectively).

Moreover, we assessed the possibility that targeted clinical surveillance of survivors of Hodgkin's lymphoma could partly account for the raised odds ratios. Table 5 shows the distribution of thyroid tumour size and whether metastasis to local lymph nodes had occurred at the time of surgery for thyroid cancer, by type of first cancer. Complete tumour staging could not be determined solely from pathology reports; however, tumour dimension (in centimetres) and information on nodal involvement was available for 61 of the 72 (85%) thyroid cancers. If several dimensions or cancers were described within the thyroid gland, the tumour or dimension of the largest size was recorded. Patients with Hodgkin's lymphoma had smaller tumours and fewer nodal metastases at the time of surgery than did those diagnosed with a first leukaemia or other types of first cancers. Our data suggested that size of the thyroid tumour at the time of diagnosis might increase with length of follow-up interval after Hodgkin's lymphoma, although the sample size was small and the trend was not significant (data not shown).

Discussion

We have shown that the risk of subsequent primary thyroid cancer after a first tumour in childhood rose with increasing radiation dose (greatest risk 20–29 Gy), but decreased at doses of more than 30 Gy. Therefore, we have shown a drop in the radiation dose-response for a solid cancer after a first cancer in childhood, consistent with a cell-killing effect of radiation at high doses.

Chemotherapy for a first tumour in childhood did not affect the risk of subsequent thyroid cancer, and did not modify the effect of radiotherapy on thyroid-cancer risk. Furthermore, we noted that thyroid tumours after a first cancer in childhood were smaller at the time of diagnosis in people who had had Hodgkin's lymphoma than in those who had had a different type of childhood cancer, suggesting an effect of heightened surveillance that detected invasive tumours earlier in their natural history.

Two previous studies[10,11] of thyroid cancer in childhood cancer survivors suggested that a linear dose-response relation did not describe the data well, but that the small number of cases did not substantiate a firm conclusion that risk unequivocally plateaued or decreased at high radiation doses. Thyroid-cancer risk in one cohort[11] was reanalysed several years later, and the investigators concluded that although the data suggested a levelling of thyroid-cancer risk at high doses, a curvilinear model was not significantly better than a linear model.[12] We saw a fall in thyroid-cancer risk at high doses (ie, >30 Gy), and that this relation was qualitatively unchanged when analysis was restricted to cases and controls with the same type of first cancer.

Analysis of those who had had a first cancer other than Hodgkin's lymphoma showed a curvilinear relation between radiation dose and risk of subsequent primary thyroid cancer, suggesting that the Hodgkin's lymphoma subgroup, which was exposed to high doses of radiation, did not solely account for the reduction in risk at the highest radiation doses. We saw this dose-response pattern in survivors younger than 10 years at first cancer diagnosis and in those 10 years or older (although the amplitude was much lower for those ⩾10 years), and thus our findings are not attributable to the least radiosensitive older patients who had cancer during childhood receiving the highest doses. These observations suggest that the drop in thyroid-cancer risk at high doses is real. Although the curvilinear dose-response relation was less pronounced for some subgroups, we think that differences in risk for radiation dose by age at diagnosis of first cancer or for characteristics unique to the type of first cancer do not explain the drop.

Our finding of increasing thyroid-cancer risk with rising therapeutic radiation dose at low doses (ie, <15 Gy) and declining risk at higher doses is consistent with the cell-killing hypothesis proposed by Louis Gray in 1964,[27] and resembles findings for leukaemia incidence after treatment for cervical cancer.[26] By contrast, results of two studies of breast[28] and lung cancer[29] after Hodgkin's lymphoma showed that second-cancer risks for both sites were linear over a wide range of radiation doses. The highest doses to the breast and lung exceeded 40 Gy and 30 Gy, respectively—ie, within the range that we observed the fall in risk of subsequent primary thyroid cancer. However, the researchers cautioned that small numbers of patients who received low doses might have diminished the ability to detect a risk reduction at doses more than 30 Gy.[28,29]

Risk of thyroid cancer in children and adolescents exposed to environmental contamination from the Chernobyl accident was linear over the dose range of up to 2·7 Gy.[30] The ERR estimate of 1·65 per Gy (95% CI 1·10–3·20) in that study[30] is consistent with our ERR of 1·32 per Gy (0·44–4·06) for doses less than 15 Gy, although residents near Chernobyl were mainly exposed to internal β radiation (ie, iodine-131) rather than external γ radiation used in radiotherapy. Despite wide CIs, the similarity of the risk estimates is of interest in view of the uncertainty about the relative biological effectiveness of these two types of radiation.[31]

Because radiotherapy induces thyroid-gland dysfunction—including hypothyroidism, Graves' hyperthyroidism, and benign nodules[32–34]—we presumed that the presence of these conditions in many of the patients who received high doses of radiation indicated that cells in the thyroid tissue were killed or that the surviving cells had lost their capacity to proliferate.[35] We analysed self-reports of thyroid-gland dysfunction from questionnaire data according to radiation dose in controls, but the numbers were too sparse for meaningful interpretation. An earlier observation[33] that no thyroid cancers occurred in patients on thyroid-replacement therapy prompted us to repeat our analyses by excluding those individuals who reported hypothyroidism before thyroid-cancer diagnosis (and the equivalent time point in controls). We found little difference in the risk estimates, and the drop in risk at high doses remained, although we acknowledge that self-reported hypothyroidism might be an imperfect surrogate measure of thyroid-hormone replacement.

Although the dose-response curves did not differ significantly by age at first cancer diagnosis, the reduction in radiation-related thyroid-cancer risk with increasing age at exposure is consistent with the findings of several previous studies.[12,17,36,37] The dose-response relation at low doses did not differ significantly between men and women, despite consistently higher risks for women in each dose category. The difference in dose-response for Hodgkin's lymphoma compared with other types of first cancer should be viewed with caution because individuals in the high-dose groups were mainly those

who had had Hodgkin's lymphoma and because most of those in the low-dose groups had other types of first cancers. Our findings accord with well established clinical observations that thyroid cancers after a first tumour in childhood are most likely to arise 10 years or later after the first primary cancer,[5,6,12,38] and that radiation-associated risks for thyroid cancer remain increased for at least 20 years.

We assessed chemotherapeutic agents and related groups of agents because their actions might affect thyroid-cancer risk.[3,4,39] For example, busulfan and cyclophosphamide can impair thyroid function,[40,41] and others (such as dactinomycin) might decrease thyroid-cancer risk.[42] We found that chemotherapy did not increase or decrease the risk of thyroid cancer, and that the risk from radiotherapy was not modified by chemotherapy. These findings are consistent with an earlier report of no effect on thyroid abnormalities within the CCSS cohort,[34] and with results of a study from the Netherlands that showed chemotherapy did not increase damage to the thyroid axis beyond that attributable to radiotherapy alone.[43] Moreover, Tucker and colleagues[11] found no association between thyroid-cancer risk after a first tumour and treatment with alkylating agents, although dactinomycin seemed to increase the risk at doses over 10 Gy. Again, however, this study was based on small numbers of patients.

We found a raised risk of thyroid cancer associated with a first diagnosis of Hodgkin's lymphoma compared with other cancers in childhood; this risk persisted after adjustment for radiation dose and age at irradiation. However, this increase might be partly attributable to the heightened detection of secondary cancer in patients who have previously had Hodgkin's lymphoma, who are often under close surveillance for thyroid abnormalities during long-term follow-up.[34,44] We are not aware of shared genetic susceptibility to both Hodgkin's lymphoma and thyroid cancer, although analyses indicate that several solid cancers (breast, ovary, kidney, uterine cervix, and brain) aggregate in family members of patients with Hodgkin's lymphoma.[45]

Data for a French cohort suggested that a first primary tumour of neuroblastoma confers increased risk of thyroid cancer after excluding the effect of treatment,[9,10,46] possibly because of a common predisposition.[47] However, this finding was not confirmed by others.[48] Although we reported an increased risk of thyroid cancer after neuroblastoma compared with leukaemia survivors, this finding was based on very small numbers (four cases and nine controls). Importantly, it should be recognised that all such analyses compare different childhood cancers with each other. Despite matching and covariate adjustment, these analyses probably cannot capture all relevant risk factors for thyroid cancer. Most notably, neuroblastoma is diagnosed at very young ages when susceptibility to radiation-induced thyroid cancer is high and therefore separating the risk of subsequent primary thyroid cancer as a result of neuroblastoma as a first primary cancer from that of age at radiation treatment is difficult.

We should emphasise that the CIs around the dose-response curves were wide even though our study was large, and the model might not describe the data well over the entire range of doses. Nevertheless, our study has many strengths, which include: detailed treatment information for the first cancer; specific radiation doses to the thyroid gland and dose to the pituitary gland; pathologically confirmed thyroid cancers; and consideration of several possible modifying factors from questionnaire data.

We conclude that at radiation doses above 30 Gy to the thyroid gland, there is evidence of a diminished risk of subsequent thyroid cancer relative to the risk at lower doses. Thus, the widely-held belief that lower doses reduce late carcinogenic effects does not necessarily apply in all instances. Although our observations are unlikely to affect treatment decisions for the first malignant disorder, there may be cause to reconsider methods of thyroid-cancer detection in those who have survived cancer in childhood and who received radiotherapy. Our data underscore the importance of yearly examination of the neck and thyroid gland in all survivors previously given radiation to the thorax or head and neck region.[34,49] We emphasise the need for surveillance, but we also acknowledge the controversy surrounding the most appropriate modality for thyroid-cancer screening in high-risk populations.[6,50] Whereas palpation of the thyroid gland might not detect some small cancers, ultrasonography will detect more neoplasms, including many small benign and malignant lesions of uncertain clinical importance. Because of the long period between treatment and development of thyroid cancer, we have confirmed the importance of long-term surveillance for survivors of cancer during childhood.

Contributors

A Sigurdson wrote the original protocol, participated in study conception and design, interpreted the data, and was mainly responsible for writing the final report. C Ronckers modelled and interpreted the data, assisted in drafting the article, and contributed to the intellectual content and critical revision of the final report. S Smith did the data acquisition and assessment of data quality, and estimated the thyroid-radiation doses. Y Liu did the data acquisition, assessment of data quality, and cohort-specific analyses. R Berkow contributed clinical expertise, participated in the study idea, and critical revision of the paper. S Hammond did pathological analysis for confirmation of thyroid cancers, contributed clinical expertise, participated in the study idea, and contributed to critical revision of the paper. L Robison, C Sklar, A Meadows, A Mertens, J Neglia, P Inskip, and M Stovall are members of the CCSS Steering Committee. They contributed to the study idea and design, expert acquisition and interpretation of data, intellectual content, and critical revisions of the paper. C Sklar also contributed clinical endocrinology expertise, M Stovall also contributed radiation-dosimetry expertise, and P Inskip also contributed to all phases of study design and implementation, data modelling and interpretation, and to preparation of the article.

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Conflict of interest statement

We declare that we have no conflict of interest.

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